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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,529	WATKINS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/18/2005; 8/4/2005; and 9/27/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-22,42-63 and 84-90* is/are pending in the application.

4a) Of the above claim(s) *3-16,18-20,44-63 and 84-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,17,21,22,42,43,89 and 90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/26/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 18, 2005, has been entered.

1. The amendment filed July 18, 2005, is acknowledged and has been entered. Claim 84 has been canceled. Claims 1, 2, 21, and 22 have been amended. Claims 84-90 have been added.

2. The amendment filed August 4, 2005, is acknowledged and has been entered. Claim 2 has been amended.

3. The amendment filed September 27, 2005, is acknowledged and has been entered. Claim 1 has been canceled. Claims 2, 17, 21, 22, 42, and 43 have been amended.

4. Claims 2-22, 42-63, and 84-90 are pending in the application. Claims 3-16, 18-20, 44-63, and 84-88 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention or species of invention, there being no allowable generic or linking claim.

5. Claims 2, 17, 21, 22, 42, 43, 89, and 90 are currently under prosecution.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Response to Amendment

8. The amendments filed July 18, 2005, August 4, 2005, and September 27, 2005, considered non-compliant because it fails to meet the requirements of 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). However, in order to advance prosecution, rather than mailing a Notice of Non-Compliant Amendment, Applicant is advised to correct the following deficiency in replying to this Office action:

The amendments are non-compliant because the status identifier of claim 3, which has been withdrawn from further consideration, does not properly indicate that status.

It appears Applicant's error may have arisen as a result of the Examiner's error in the Office action mailed February 16, 2005, as it is noted the Examiner did not list claim 3 as withdrawn from consideration in section 2 at page 2 of that Office action, but nevertheless did not examine claim 3. In the interest of advancing prosecution, Applicant has been advised of this error in lieu of mailing a Notice of Non-Compliant Amendment, per MPEP § 714.03(c), which provides the Examiner discretion to proceed in such instances.

Election/Restrictions

9. Newly submitted claims 84-88 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The elected species of invention is a grafted antibody comprising the CDRs having the amino acid sequences set forth as SEQ ID NO: 45, SEQ ID NO: 155, SEQ ID NO: 63, SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77. In contrast, the

newly submitted claims 84-88 are directed to an antibody comprising the CDRs having the amino acid sequences set forth as amino acids 6-10 of SEQ ID NO: 45, SEQ ID NO: 155, SEQ ID NO: 63, SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77. Accordingly, newly submitted claims 84-88 are drawn to a species of antibody that differs structurally from the elected species of antibody; because the antibody to which claims 84-88 is structurally different from the elected species of antibody, the search required to examine claims 84-88 is not the same, nor is it coextensive with the search that has already been performed to permit examination of claims directed to the elected species. Therefore, an separate and additional new search would have to be performed to examine claims 84-88; and the need to perform such an additional search would constitute a serious burden.

Since Applicants have received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for further prosecution on the merits. Claims 84-88 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR § 1.142(b) and MPEP § 821.03.

10. Applicant's remarks at pages 15 and 16 of the amendment filed July 18, 2005 are acknowledged.

In response, as noted at page 7, section 14, of the Office action mailed October 21, 2003, the examiner required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Furthermore, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

In further response to Applicant's remarks, as noted at beginning at page 2 in section 5 of the Office action mailed May 11, 2004, upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, Applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Grounds of Objection and Rejection Withdrawn

11. Unless specifically reiterated below, the amendments and/or arguments accompanying the amendments filed July 18, 2005, August 4, 2005, and/or September 27, 2005, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed February 16, 2005.

New Grounds of Rejection

Claim Rejections – 35 USC § 112

12. Claims 2, 17, 21, 22, 42, 43, 89, and 90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** an antibody, or a functional fragment thereof, which has at least a two-fold higher binding activity for denatured collagen over native collagen, wherein said antibody or functional fragment comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO: 46, SEQ ID NO: 28, and SEQ ID NO: 63 and wherein said antibody or functional fragment comprises the three light chain CDRs of SEQ ID NO: 20, SEQ ID NO: 22, and SEQ ID NO: 77, and a nucleic acid molecule encoding said antibody, **does not reasonably provide enablement for making and using** an antibody or a functional fragment thereof that has at least a two-fold higher binding activity for denatured collagen over native collagen, wherein said antibody or functional fragment comprises the three heavy chain CDRs of SEQ ID NO: 45, SEQ ID NO: 155, and SEQ ID NO: 63 and wherein said antibody or functional fragment comprises the three light chain CDRs of SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77, or any other variant of monoclonal antibody HUIV26, which is encompassed by the generic claims, or any nucleic acid molecule encoding said antibody or other variant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue experimentation.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person

skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The claims are directed to a genus of antibodies or functional fragments thereof an antibody, or a functional fragment thereof, which has at least a two-fold higher binding activity for denatured collagen over native collagen.

The elected species of the claimed invention is the antibody, or functional fragment thereof, which comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO: 45, SEQ ID NO: 155, and SEQ ID NO: 63 and the three light chain CDRs of SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77.

The specification teaches two variants of monoclonal antibody HUIV26, which have the requisite preferential binding activity for denatured collagen over native collagen, namely "2D4H1-C3" and "DhuG5"; see, e.g., Figure 8. Monoclonal antibody HUIV26 lacks this preferential binding activity, as it does not bind with any substantially greater affinity to denatured collagen over native collagen. Accordingly, it is evident that the structural variation (i.e. amino acid substitutions), which characterizes the variants, must account for the differential binding activity of the variants as compared to monoclonal antibody HUIV26.

The first of these variants comprises a heavy chain variable region comprising the first, second, and third CDRs of SEQ ID NO: 46, SEQ ID NO: 28, AND SEQ ID NO:

63, respectively, and a light chain variable region comprising the first, second, and third CDRs of SEQ ID NO: 20, SEQ ID NO: 22, and SEQ ID NO: 77. However, the specification does not appear to describe the variant "DhuG5", such that it is evident which, if any, of the disclosed amino acid sequences represent its CDRs. As such, the skilled artisan could not make the variant of monoclonal antibody designated "DhuG5"; therefore, the only variant demonstrated to have the requisite preferential binding activity for denatured collagen over native collagen, which could be made, is that designated "2D4H1-C3".

The specification does not demonstrate the elected species of antibody (i.e., the antibody, or functional fragment thereof, which comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO: 38, SEQ ID NO: 40, and SEQ ID NO: 103 and the three light chain CDRs of SEQ ID NO: 32, SEQ ID NO: 34, and SEQ ID NO: 36) to have at least 2-fold greater binding activity for denatured collagen, as compared to its binding activity for native (non-denatured) collagen. Although the elected species of antibody comprises a heavy chain variable region comprising the same third CDR as the variant designated "2D4H1-C3", which has the requisite preferential binding activity for denatured collagen, the heavy chain of the elected species of antibody comprises a different first and second CDR (i.e., a CDR1 having the amino acid sequence set forth as SEQ ID NO: 45, as opposed to the amino acid sequence of SEQ ID NO: 46, and a CDR2 having the amino acid sequence set forth as SEQ ID NO: 155, as opposed to the amino acid sequence of SEQ ID NO: 28). Furthermore, although the elected species of antibody comprises a light chain variable region comprising the same second and third CDRs as the variant designated "2D4H1-C3", the light chain comprises a different first CDR (i.e., a CDR1 having the amino acid sequence set forth as SEQ ID NO: 157, as opposed to the amino acid sequence of SEQ ID NO: 20). The only structurally different features that might account for any differential binding activity, as compared to monoclonal antibody HUIV26, which is shared by the variant designated "2D4H1-C3" and the elected species of invention is the identity of the third CDR of the heavy chain and the identity of the third CDR of the light chain. While it would be understood that that variation in one or both of the first

and third CDRs of the heavy chain and/or the variation in the third CDR of the light chain of the variant designated "2D4H1-C3" must account for the observed differential binding activity of the variant, as compared to monoclonal antibody HUIV26 (see, e.g., Figure 8), it is not known, and cannot be predicted whether the variation in the third CDR of the heavy chain alone might account for this differential binding activity. For this reason, it is not known, and cannot be predicted whether the elected species of invention will also have such preferential binding activity for denatured collagen over native collagen, as compared to monoclonal antibody HUIV26, which does not have such preferential binding activity. Moreover, it cannot be predicted whether any of the other disclosed variants of monoclonal antibody "2D4H1-C3" have at least 2-fold greater binding activity for denatured collagen, relative to its binding activity for native collagen; for this reason, the claimed invention cannot be made and/or used without undue and/or unreasonable experimentation because it would be necessary to first make a variant of monoclonal antibody HUIV26, which might be encompassed by the claims, and then empirically determine whether it has the requisite binding activity.

Thus, while the skilled artisan has an understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is nevertheless characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains (particularly, within the complementarity determining regions (CDRs)) and surrounding framework regions of antibodies. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA.* 1987 May; **84** (9): 2926-2930) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*Proc. Natl. Acad. Sci. USA.* 1989 Jul; **86** (14): 5532-5536) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the

primary structure of an antibody, including substitutions as a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*Mol. Immunol.* 2003 May; **39** (15): 941-952) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

As a consequence of the lack of predictability in the art of antibody engineering, it is evident that undue and/or unreasonable experimentation would have to be performed before the claimed invention, reasonably commensurate in scope with the claims, could be made and/or used successfully by the skilled artisan, since, as evidenced by Caldas et al., for example, the skilled artisan cannot reliably and accurately predict the consequences of amino acid substitutions, insertions and deletions in the CDRs of monoclonal antibody HUIV26 upon the structure and function of an antibody comprising such altered heavy and light chain variable regions. Given the teachings of Giusti et al. (cited *supra*), for further exemplification, it is apparent that even a single amino acid substitution in the primary structure of the heavy chain variable region of an antibody can change both the affinity and specificity of the antibody.

Moreover, although it may be well within the skill of the artisan to graft the three CDRs from both the light and heavy chain variable regions of the disclosed variant of monoclonal antibody designated "2D4H1-C3", which has the requisite binding activity, into the framework of, e.g., a human antibody without substantial loss of that requisite affinity and specificity, the claims are not limited to such engineered antibodies, since the claims are directed to a far broader genus of structurally different antibodies, or functional fragments thereof, having one or more amino acid substitutions within the CDRs if such a variant. Again, as evidenced by Caldas et al. (*supra*), for example, the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions within the antigen-binding domains of an antibody, or more particularly within the CDRs.

It is noted that the specification discloses in the table set forth as Figure 4C the amino acid substitutions that were found to be "beneficial" following the introduction of

random mutations in the CDRs of either the light or heavy chain variable regions of the Fab of monoclonal antibody HUIV26 (i.e., "wild-type Fab"). The specification discloses such "beneficial" mutations are those producing antibodies binding denatured collagen with higher affinity, relative to the corresponding wild-type Fab, as demonstrated by ELISA; see, e.g., page 87, lines 12-15. The table, for example, indicates that certain substitutions of the amino acid at position 35 of the first CDR of the heavy chain polypeptide of monoclonal antibody HUIV26 (i.e., the amino acid at position 10 within the amino acid sequence of the CDR set forth as SEQ ID NO: 26) are "beneficial", such as the replacement of the naturally occurring serine at this position by threonine, alanine or glycine. In comparison, the claims are directed to a genus of variants of monoclonal antibody HUIV26, which includes but are not limited to a variant comprising a heavy chain comprising a first CDR having the amino acid sequence set forth as SEQ ID NO: 45 (i.e., a heavy chain CDR1 having the amino acid sequence of SEQ ID NO: 26 but for substitution of the amino acid at position 10 by threonine), as the claims also encompass variants comprising a heavy chain comprising a first CDR having the amino acid sequence of SEQ ID NO: 26 but for substitution of the naturally occurring serine at position 10 by "any conservative substitution" of serine. As disclosed by the specification at page 21, lines 24-31, *exemplary* conservative substitutions of serine include cysteine, methionine, threonine, asparagine, and glutamine. As such, it is duly noted that substitution of the serine at position 35 within the first CDR of the heavy chain of wild-type Fab (i.e., position 10 of CDR1 having the amino acid sequence set forth as SEQ ID NO: 26) by glycine, which is disclosed as a "beneficial" mutation, might not be considered a conservative substitution. Similarly substitution of the amino acid at position 34 of the first CDR (i.e., a methionine, which occurs at position 9 of SEQ ID NO: 26) by isoleucine, which according to the table of Figure 4C is also a "beneficial" mutation, would not ordinarily be considered a conservative substitution, given the fact that substitutions by amino acids having different chemical properties are not generally regarded as "conservative". The different chemical properties of methionine and isoleucine are evident in view of the disclosure at page 21, lines 24-31, that methionine is a "polar" amino acid, whereas isoleucine is "non-polar". Despite the fact that this

"beneficial" substitution of the methionine at this position or the "beneficial" substitution of the serine at position 35 by glycine within the first CDR of the heavy chain is not conservative, per se, the claims are directed to a genus of antibodies having a heavy chain comprising a first CDR having the amino acid sequence of SEQ ID NO: 38 but for substitution of the naturally occurring methionine or serine at positions 6 and/or 7 by "any conservative substitution" of methionine and serine, respectively; and yet there is insufficient factual evidence of record that would support the assertion that such substitutions of this methionine or this serine would be found "beneficial", or produce an antibody having the requisite binding activity for denatured collagen over native collagen, as compared to wild-type Fab. To the contrary, there appears to be factual basis for concluding that *non-conservative* substitutions of this methionine by isoleucine and *non-conservative* substitutions of this serine by glycine produce a variant of monoclonal antibody HUIV26 having higher affinity, relative to the corresponding wild-type Fab, as demonstrated by ELISA. These results underscore the unpredictable nature of the art of antibody engineering that has been shown by the disclosures of Giusti et al, Chien et al., and Calabas et al. (all cited *supra*).

In addition, it is noted that according to the table set forth as Figure 6, only certain "combinatorial mutants", which are variants of wild-type Fab (i.e., the Fab of monoclonal antibody HUIV26) comprising more than one of the "beneficial" substitutions identified by random mutagenesis, are disclosed as having equivalent or enhanced binding activity, as compared to wild-type Fab. None of these "combinatorial mutants" however appear to be disclosed as having, per se, at least 2-fold greater binding activity for denatured collagen over native collagen. Furthermore, as the "combinatorial mutants" disclosed in Figure 6 as having equivalent or enhanced binding activity comprise only the one or two substitutions in one or more of the CDRs of the light and/or heavy chain variable regions of monoclonal antibody HUIV26, which are specifically iterated in the claims, it is not known, nor can it be predicted whether such variants having amino acid sequences with only one or two of such substitutions have the requisite binding activity. Moreover, many of the "combinatorial mutants", which are specifically encompassed by the claims, have not been shown to have the requisite

binding activity, and undue and/or unreasonable experimentation would therefore be necessary before the claimed invention could be used, as it cannot be predicted whether these "combinatorial mutants" will have the requisite binding activity.

In addition, it is noted that claims 21 and 22 are directed to a genus of antibodies or functional fragments thereof comprising a heavy chain polypeptide or a light chain polypeptide, respectively. As noted in the preceding Office action, antibodies having the requisite binding activity must comprise both a heavy chain polypeptide and a light chain polypeptide, as each provides three CDRs, which are critical determinants of the ability of an antibody to bind an antigen. "Antibodies" or functional fragments thereof comprising only one or the other will not bind an antigen; furthermore, while this fact would be understood by the skilled artisan, the claims must be given the broadest reasonable interpretation that is both consistent with the disclosure and that which would be given the claims by the skilled artisan. The specification teaches antibodies comprising light and heavy chain polypeptides, which bind denatured collagen, but this amount of guidance, direction, and enablement is not reasonably commensurate in scope with the claims, as again the claims encompass antibodies that bind preferentially to denatured collagen, which comprise only a light chain, such as those disclosed, or a heavy chain, such as those disclosed, but not necessarily both. Undue and unreasonable experimentation would be required before the skilled artisan could identify other suitable light or heavy chain polypeptides derived, for example, from other antibodies differing from those disclosed (i.e., monoclonal antibody HUIV26), which could be used to make the claimed invention.

Finally, it is noted that claims 89 and 90 are directed to a genus of antibodies comprising the heavy chain CDR1, CDR2, and CDR3 of SEQ ID NO: 45, SEQ ID NO: 155, SEQ ID NO: 63, respectively, and the light chain CDR1, CDR2, and CDR3 of SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77, respectively, but neither claim recites that the members of the genus necessarily have any particular binding activity. Given the broadest, reasonable interpretation that is consistent with the disclosure and that of the skilled artisan, the claims are directed to a genus of functionally different antibodies. At best, the specification should only be considered reasonably enabling for members of

the claimed genus of antibodies that have or retain the binding specificity of the disclosed antibodies (e.g., monoclonal antibody HUIV26), which binds denatured collagen. If members of the claimed genus do not have or retain such binding activity, undue and unreasonable experimentation would be required to use the invention, as it would be necessary to determine the antigen to which such functionally different antibodies bind before they could be used.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

13. Claims 2, 21, 22, 42, and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Claims 2, 21, 22; 42, and 43 are directed to a genus of antibodies, or functional fragments thereof that include numerous members that do not appear to find written support in the specification, including the claims, as originally filed. Claim 2, for example, is directed to a genus of antibodies or functional fragments thereof that comprise a heavy chain polypeptide comprising a first complementarity determining region (CDR), which has the amino acid sequence of SEQ ID NO: 26 or a variant thereof (e.g., a CDR having the amino acid sequence of SEQ ID NO: 26 but for substitution of the amino acid at position 6 with "a conservative substitution of R", substitution of the amino acid at position 9 with "a conservative substitution of M" and substitution of the amino acid at position 10 with "a conservative substitution of S". In

addition, claim 2 is directed to such an antibody comprising a heavy chain polypeptide that further comprises a second CDR, which has the amino acid sequence of SEQ ID NO: 28 or has an amino acid sequence that is a variant thereof having "a conservative substitution" of the amino acid at, e.g., position 9, or which further comprises a third CDR, which has the amino acid sequence of SEQ ID NO: 30 or has an amino acid sequence that is a variant thereof having "a conservative substitution" of the amino acid at, e.g., position 3. According to claim 2, the light chain of these members of the claimed genus comprise a light chain polypeptide comprising a first, second, and third CDR, which have, e.g., the amino acid sequence of SEQ ID NO: 20 or a variant thereof having a conservative substitution of the native amino acid at positions 4, 8, 10, and/or 12, the amino acid sequence of SEQ ID NO: 22, and the amino acid sequence of SEQ ID NO: 24 or a variant thereof having a conservative substitution of the native amino acid at positions 5 and/or 6, respectively. As another example, claim 21 is directed to a genus of antibodies or functional fragments thereof that comprise a heavy chain polypeptide comprising a first complementarity determining region (CDR), which has the amino acid sequence of SEQ ID NO: 45 or a variant thereof (e.g., a CDR having the amino acid sequence of SEQ ID NO: 45 but for substitution of the amino acid at position 6 with "a conservative substitution of R", substitution of the amino acid at position 9 with "a conservative substitution of M", and substitution of the amino acid at position 10 with "a conservative substitution of S". According to claim 21, the heavy chain of these members of the claimed genus further comprise a second and third CDR, which have, e.g., the amino acid sequence of SEQ ID NO: 155 or a variant thereof having a conservative substitution of the native amino acid at positions 9, 14, and/or 17 and the amino acid sequence of SEQ ID NO: 63 or a variant thereof having a conservative substitution of the native amino acid at positions 3, 4, and/or 11, respectively. Claim 22 is similarly drawn to a genus of antibodies or functional fragments thereof that comprise a light chain polypeptide comprising a first CDR, or variant thereof, a second CDR, or a variant thereof, and a third CDR, or variant thereof.

At page 23 of the amendment filed September 27, 2005, Applicant has remarked that written support for the genus of antibodies and functional fragments, which are

specifically iterated in the present claims, find written support in the sequences found throughout the Sequence Listing and elsewhere in the specification (e.g., at paragraphs [0049] to [0051] of the published application); however, it does not appear that the amendment indicates with particularity where in the specification, including the claims, as originally filed, written support for each of these particular members of the claimed genus of antibodies and functional fragments thereof is found.

Paragraphs [0049] to [0051] of this published application correspond to the paragraphs at page 24, lines 26, through page 28, line 2, of the instant specification. However, none of these paragraphs appear to provide written support for the specific genus of antibodies and functional fragments thereof, which are iterated in the present claims, since, e.g., none describe variants of monoclonal antibody HUIV26 comprising a heavy chain polypeptide comprising a first CDR having an amino acid sequence that is a variant of the amino acid sequence set forth as SEQ ID NO: 26 having a conservative substitution of the native amino acid at position 6, per se. The amino acid at position 6 of SEQ ID NO: 26 is arginine (i.e., "R") and corresponds to the amino acid at position 31 of amino acid sequence of the variable region of the heavy chain of monoclonal antibody HUIV26, as depicted in Figure 2C; and as disclosed at page 21, lines 24-31, exemplary conservative substitutions of arginine include lysine and histidine. However, the specification, including the claims, as originally filed, does not teach or suggest substituting, in particular, the amino acid at position 6 of first CDR of monoclonal antibody HUIV26 (i.e., SEQ ID NO: 26) with any "conservative substitution" of arginine, including, in particular, lysine, nor does it particularly teach or suggest substituting this amino acid for any amino acid other than histidine (see, e.g., Figure 4C). Moreover, although the disclosure at page 24, line 26, through page 25, line 32, describes specific variants of monoclonal antibody HUIV26, which comprise one or more CDRs having amino acid sequences that vary from those of the native light and heavy chain polypeptides, this disclosure does not provide written support for each of the particularly claimed members of the genus of antibodies and functional fragments thereof, which comprise a "conservative substitution" of any one particular naturally occurring amino acid in one or more of the CDRs of either one or both of the light and heavy chain

variable regions of monoclonal antibody HUIV26. The disclosures at p page 24, line 26, through page 25, line 32, might arguably provide sufficient support for a genus of antibodies and functional fragments that comprise light or heavy chain polypeptides comprising one or more CDRs having amino acid sequences that are variants of those naturally occurring due to one or more amino acid substitutions, but these disclosure do not appear to suffice to adequately provide written support for each of the particularly claimed members of the genus created by "conservative substitutions" at particular positions within the CDRs.

In addition, while the specification might arguably provide written support for a genus of antibodies and functional fragments comprising one or more CDRs having amino acid sequences that are substitution variants of those naturally occurring in monoclonal antibody HUIV26, which have or retain binding specificity for denatured collagen, such as at page 28, lines 18-21, it does not appear that the specification provides adequate written support for the claimed genus of antibodies and functional fragments produced by conservative substitutions at such particular positions within the CDRs, which have, per se, at least a 2-fold greater binding activity for denatured collagen, compared to the binding activity for native (non-denatured) collagen. The specification describes only two variants of monoclonal antibody HUIV26 having such preferential binding activity for denatured collagen, namely "2D4H1-C3" and "DhuG5"; see, e.g., Figure 8. On the other hand, the specification does not appear to describe the members of the claimed genus as commonly sharing such preferential binding activity for denatured collagen, as again it only appears to describe the members as having or retaining binding specificity for a "cryptic collagen epitope" (see, e.g., page 28, lines 18-21).

For these reasons, the amendments filed in reply to the preceding Office action appear to introduce new matter, thereby violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

This issue might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the present claims.

14. Claims 2, 17, 21, 22, 42, 43, 89, and 90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

As explained in the "new matter" rejection the claims are directed to a genus of antibodies, or functional fragments thereof, which are variants of monoclonal antibody HUIV26 having at least 2-fold greater binding activity for denatured collagen over native collagen; however, the specification, including the claims, as originally filed, does not appear to provide written support for such claims. As such, the specification does not adequately describe the claimed genus in such as way as to permit the skilled artisan to immediately envision, recognize or distinguish at least a substantial number of its members and thereby reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

For example, while the specification adequately describes the variant designated "2D4H1-C3" as having the requisite binding activity, no other member of the claimed genus, such as the elected species of invention, is so described.

In deciding *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997), the Federal Circuit held that a generic statement that defines a genus of nucleic acids *by only their functional activity* does not provide an adequate written description of the genus. By analogy, a generic statement that defines a genus of antibodies or functional fragments thereof by only their common ability to bind

denatured collagen with higher affinity than native collagen does not serve to adequately describe the genus as whole. The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). Without the antibodies to which the claims are directed, it is impossible to make or use the claimed invention.

In addition, although the skilled artisan could potentially screen candidate antibodies to identify antibodies are encompassed by the claims, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v.*

Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

With further regard to claims 89 and 90, the claims do not require the members of the claimed genus of antibodies or functional fragments thereof to have any particular function. As such, the claims are directed to a genus of structurally and functionally variable antibodies; although the antibodies necessarily comprise particular structural elements (i.e., heavy chain CDRs of SEQ ID NOs: 45, 155, and 63 and light chain CDRs of SEQ ID NOs: 157, 22, and 77), because the function of the antibodies may vary, there is no particularly identifying structural feature that corresponds to a particularly identifying functional feature, so as to permit the skilled artisan to immediately envision, recognize or distinguish members of the claimed genus from other antibodies and functional fragments thereof.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of antibodies, which vary structurally, such that there is no correlation between any one particularly identifying structural feature and their common functional feature, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that

Applicant was in possession of the claimed invention at the time the application was filed.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
December 27, 2005